REMARKS

Reconsideration of this application is requested in view of the foregoing amendments and following remarks.

I. Claim Amendments

Prior to entry of the foregoing amendment, claims 1-28 were pending.

Claims 2-7 and 23-28 are requested to be cancelled without disclaimer or prejudice to further prosecution on the merits.

Claim 1 is currently amended effectively to incorporate the limitations of claims 6, 7, 24, and 25. As amended, claim 1 recites "[a] method of increasing rate of skeletal repair in a mammal having a bone implant or bone transplant by stimulating osteoblast-mediated growth of new bone at the site of the transplant or implant, comprising administering to the mammal at the site of the implant or transplant, in an immobilized, slow release form, a therapeutically effective amount of a compound having the formula..." The amendments to claim 1 are supported fully in the original specification and claims. For example, the specification states:

> It has now been found that 2-carbon-modified vitamin D compounds can markedly ***stimulate the formation of new bone when added to primary cultures of osteoblasts*** and its precursors....As a result, these compounds can be used to markedly increase the ***rate of skeletal repairs*** such as repair of fractures, ***osseointegration of transplants, and the solidification of implants*** as well as acceleration of and improvement of bone quality following distraction osteogenesis procedures....The present invention is thus directed toward various pharmaceutical uses for 2-carbon modified analogs of vitamin D compounds ***which involve the formation of new bone***.

(*See* Specification, page 4, line 16 to page 5, line 4 at SUMMARY OF THE INVENTION (emphasis added)).

The present specification also states:

> One can envision providing 2MD in a ***slow-release form at the site of the fracture***; thereby providing a slow-release form such as 2MD 25-acetate or in an osmotic minipump to deliver a small amount of this compound each hour, or could be ***implanted in an immobilized form or injected in an immobilized form into the fracture area***.

(*See* Specification, page 31, lines 5-9 (emphasis added)). Original claims 6 and 7 state:

> 6. The method of claim 1 wherein the compound is administered ***in an immobilized form at a site where growth of new bone is desired***.
>
> 7. The method of claim 1 wherein the compound is administered ***in a slow release form at a site where growth of new bone is desired***.

Therefore, the amendments to claim 1 are fully supported by the original specification and claims and do not introduce new matter.

Claims 29-32 are requested to be added. Claim 29 recites subject matter related to the subject matter recited in claim 1. However, where claim 1 recites "a compound in an immobilized, slow release form at the bone fracture," claim 29 recites "a compound in an immobilized form at the bone fracture." Claim 30 depends from claim 29 and recites subject matter related to the subject matter recited in original claim 10.

Claim 31 recites subject matter related to the subject matter recited in claim 1. However, where claim 1 recites "a compound in an immobilized, slow release form at the bone fracture," claim 31 recites "a compound in a slow release form at the bone fracture." Claim 32 depends from claim 31 and recites subject matter related to the subject matter recited in claim 10.

After entry of the foregoing amendments, claims 1, 8-22, and 29-32 are pending.

II. Summary of Claimed Subject Matter

The present claims have been amended to recite "[a] method of increasing rate of skeletal repair in a mammal having a bone implant or bone transplant by stimulating osteoblast-mediated growth of new bone at the site of the transplant or implant, comprising administering to the mammal at the site of the implant or transplant, in an immobilized, slow release form, a therapeutically effective amount of a [2-carbon-modified vitamin D compound]." As such, the claimed subject matter relates to a method of administering 2-carbon-modified vitamin D compounds to a ***specific*** group of patients (*i.e.*, patients having bone implants or transplants), in a ***specific*** manner (*i.e.*, in an immobilized and/or slow-release form at the site of the implant or transplant), for a ***specific*** reason (*i.e.*, to increase the rate of skeletal repair by stimulating osteoblast-mediated growth of new bone at the site of the transplant or implant). None of the cited references explicitly or inherently discloses or suggests the claimed method.

Furthermore, the present inventors are the first to show that 2-carbon-modified vitamin D compounds such as compound 2MD can be used to stimulate osteoblasts to form new bone (*i.e.*, as anabolic bone agents). The Von Kossa stain results presented in the application and illustrated in Figure 2 indicate that 2MD stimulates osteoblasts to form new bone. (*See, e.g.*, specification, page 30, lines 16-18, (stating that the results in Figure 2 "clearly demonstrate that 2MD has a unique and strong action on stimulating the osteoblast cultures to form mineralized bone as revealed by the Von Kossa stain")).

Not all vitamin D compounds will stimulate osteoblasts to form new bone. Until the present inventors demonstrated that 2MD could be used to grow new bone (*i.e.*, that 2MD was an anabolic bone agent), there was no motivation to administer 2MD in a manner intended to stimulate the formation of new bone at the site of a bone transplant or bone implant (*i.e.,* in an immobilized and/or slow release form) and there was no reasonable expectation of success that 2MD could be used to increase the rate of skeletal repair. Therefore, the claimed method is not obvious over the cited references.

III. Double Patenting – 35 U.S.C. § 101

Claims 1-28 stand provisionally rejected for double-patenting under 35 U.S.C. § 101 over the claims of copending Application No. 10/105,826. The rejection is a provisional rejection because the allegedly conflicting claims in the two applications have not in fact yet been patented. The Applicants respectfully traverse the rejection in view of the foregoing claim amendments and for the following reasons.

The present claims relate to methods of increasing rate of skeletal repair in subjects having bone implants or bone transplants. In contrast, the claims in copending Application No. 10/105,826 (hereinafter "the '826 application") relate to methods of "increasing the rate of repair for a bone fracture." Applicants direct the present Examiner to the restriction requirement issued for the '826 application, dated June 20, 2003 (EXHIBIT 1). In the restriction requirement, methods of stimulating healing of a bone fracture were deemed to be a separate invention from methods of stimulating healing of a bone transplant or bone implant. Therefore, it is inconsistent with the issued restriction requirement now to reject the present claims for double-patenting over the claims of the '826 application.

Reconsideration and withdrawal of the rejection are requested.

IV. Claim Rejections – 35 U.S.C. § 102

The claims stand rejected for allegedly being anticipated under 35 U.S.C. § 102 by one or more references including DeLuca *et al.* (WO 98/41501) (hereinafter "DeLuca WO '98"), U.S. Patent No. 5,945,410 (hereinafter "DeLuca '410"), and Deluca *et al.* (WO 02/05823) (hereinafter "DeLuca WO '02"). In particular, claims 1-5, 8-11, 20, 22, 23, and 25 stand rejected over DeLuca WO '98; claims 1-5, 8, 9 and 21 stand rejected over DeLuca '410; and claims 1-5, 8, 9, 20, and 22-25 stand rejected over DeLuca WO '02. The Applicants respectfully traverse the rejections in view of the foregoing claim amendments and for the following reasons.

The Office Action does not find that claims 6 or 7 are anticipated by any cited reference. Claims 1 and 8-22 have been amended effectively to incorporate the limitations of claims 6, 7, 24, and 25. New claims 29 and 30 effectively incorporate the limitations of claims 6, 24, and 25. New claims 31 and 32 effectively incorporate the limitations of claims 7, 24, and 25.

Therefore, the cited references do not anticipate the claims as amended and the rejections under 35 U.S.C. § 102 over DeLuca WO '98, DeLuca '410, and DeLuca WO '02 should be withdrawn.

V. Claim Rejections – 35 U.S.C. § 103 – DeLuca '928 in view of DeLuca WO '97

Claims 1, 6, 7, 11, and 12-19 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over DeLuca (U.S. Patent No. 5,843,928) (hereinafter DeLuca '928) in view of DeLuca (WO 97/11053) (hereinafter DeLuca WO '97). The Applicants respectfully traverse the rejection in view of the foregoing claim amendments and for the following reasons.

The present claims have been amended to require that the recited compound be administered in a ***specific*** form (*i.e.*, in an immobilized and/or slow release form), at a ***specific*** site (*i.e.*, at the site of bone transplant or implant), for a ***specific*** purpose (*i.e.*, to increase the rate of skeletal repair in a subject having a bone transplant or implant). None of the cited references teach or suggest the claimed method.

First, there is not a teaching, suggestion, or motivation in the cited references to administer the 2-carbon-modified vitamin D compounds in the recited form (*i.e.*, immobilized and/or slow release form), at the recited site (*i.e.*, at the site of bone transplant or implant), for the recited purpose (*i.e.*, in order to increase the rate of skeletal repair in a subject having a bone transplant or implant). Compounds such as 2MD may be administered in enumerable forms, in enumerable ways, for enumerable purposes. Until Applicants' present observation that 2MD can be used to stimulate bone growth,

one skilled in the art would have no reason to administer 2MD at the site of a bone transplant or bone implant in an immobilized and/or slow release form in order to increase the rate of skeletal repair. It is not permissible to use hindsight in presenting a *prima facie* case of obviousness.

Second, administering a compound "for the treatment of diseases where bone formation is desired" is not the same as administering the compound to stimulate the formation of new bone. In order to stimulate the formation of new bone, a compound must be administered in a ***specific*** manner that is not taught or suggested by the cited reference. In particular, anabolic bone agents must be administered in an immobilized, slow release form in order to be effective.

Those skilled in the art recognize that new bone formation requires that a drug be ***retained and released slowly at a fracture site***. (*See* EXHIBIT 2, Saito *et al.*, ADVANCED DRUG DELIVERY SYSTEMS 57 (2005) 1037-1048, at page 1039, last partial paragraph of left hand column, stating that "[d]elivery systems that retain BMP and release it slowly, as well as serving as scaffolding for new bone formation are essential (emphasis added)".) Others have recognized the importance of retention and slow release at the site of action. (*See, e.g.*, EXHIBIT 3, Samartzis *et al.*, J. AM. COLL. SURG., (2005) Vol. 200. No. 2, pages 236-248, at page 243, (stating that "the carrier should maintain a certain effective threshold concentration of BMP [and] the carrier should be able to contain the BMP and not allow for extraneous bone formation"); EXHIBIT 4, Seeherman *et al.*, CYTOKINE & GROWTH FACTOR REVIEWS 16 (2005) 329-345, at page 300-331, (under heading "2.1. BMP retention at the treatment site," demonstrating retention and slow release profiles for BMP); EXHIBIT 5, Termaat *et al.*, J. BONE & JOINT SURG. (2005), Vol. 87-A, No. 6, 1367-1378, at page 1371 (under heading "Carriers" stating that "[t]he primary function of these delivery materials is to increase the efficacy of BMPs by preventing rapid diffusion of the inductive agent away from the implant site and by providing a sustained release of the protein"). Therefore, those skilled in the art recognize that new bone formation by anabolic

bone agents such as bone morphogenetic proteins (BMPs) requires retention (*i.e.*, immobilization) and slow release. Others have recognized that transforming growth factor beta (TGF-β), osteoblast-stimulating factor-1/pleiotrophin (PTN), insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), and platelet-derived growth factor (PDGF), all require carrier systems that immobilize the growth factor and provide controlled delivery for effective use as bone growth agents. (*See* EXHIBIT 6, Rose *et al.*, JOURNAL OF PHARMACY AND PHARMACOLOGY, 2004, 56:415-427, at page 417 under heading "*Carrier Systems*.") These teachings related to carriers for BMPs and other anabolic bone agents are applicable to carriers for 2MD.

Therefore, prior to the inventors' observation that 2MD can be utilized to stimulate the formation of new bone, one skilled in the art would not have been motivated to administer 2MD in an immobilized, slow release form at the site of a bone implant or bone transplant. Furthermore, unless 2MD is administered in an immobilized, slow release form at the site of a bone implant or transplant, then one skilled in the art would not have a reasonable expectation of success for increasing the rate of skeletal repair at the site of the bone transplant or bone implant.

One skilled in the art also understands that not all vitamin D compounds are bone anabolic agents. (*See, e.g.*, EXHIBIT 7, Underwood *et al.*, AM. J. PHYSIOL. 1983, E493-E498, demonstrating that vitamin D does not directly stimulate osteoblasts to form new bone but does effect calcium mobilization and remodeling of bone). The compounds listed in EXHIBITS 9-12 have been observed to stimulate osteoblasts to form new bone. In contrast, the compounds listed in EXHIBITS 13-16 have not been observed to stimulate osteoblasts to form new bone. The cited references do not disclose that 2-carbon-modified vitamin D compounds can be used to stimulate osteoblasts to form new bone. Therefore, the cited references do not anticipate or render obvious the claimed subject matter.

In regard to the cited references disclosing the use of vitamin D compounds for "improvement of bone grafts," the Applicants note that "improvement of bone grafts"

does not necessarily mean "increasing rate of skeletal repair," as recited in the claims. For example, improvement of bone grafts can mean improvement in the ***quality*** of the new bone (*e.g.*, during a remodeling phase of bone healing), rather than an increase in rate of skeletal repair (*e.g.*, during a reactive or reparative phase of bone healing). Until Applicants' present observation that 2MD can be used to stimulate bone growth, one skilled in the art would not have had a reasonable expectation of success in achieving an increase in the rate of skeletal repair for a bone transplant or implant.

Healing of bone occurs in several phases which typically include:

(1) a reactive phase further divided into
  (i) a fracture and inflammatory phase; and
  (ii) a granulation tissue formation phase;
(2) a reparative phase further divided into
  (i) a callus formation phase; and
  (ii) a lamellar bone deposition phase; and
(3) a remodeling phase.

(*See* EXHIBIT 17, Wikipedia article entitled "Bone healing").

During the reactive phase, extravascular blood cells form a blood clot at the fracture and die except for surviving fibroblast cells. Subsequently, the fibroblast cells form a loose aggregated of cells known as "granulation tissue."

During the reparative phase, fibroblasts in the granulation tissue develop into chondroblasts and form hyaline cartilage. In addition, periosteal cells proximal to the fracture gap develop into chondroblasts to form hyaline cartilage. Periosteal cells distal to the fracture gap develop into osteoblasts and form "woven bone." Osteoblasts also form "new lamellar bone" which replaces the woven bone and hyaline cartilage at the fracture site. The new lamellar bone forms on the surface of mineralized matrix and is in the form of "trabecular bone." After all of the woven bone and cartilage are replaced by new

lamellar bone in the form of trabecular bone, much, if not all, of the bone's original strength is restored. (*See id.*)

During the remodeling phase, the lamellar bone is replaced with compact bone. The process includes resorption of trabecular bone by osteoclasts and deposition of compact bone by osteoblasts at the site of resorption.

Therefore, bone healing includes several phases and not all aspects involve stimulating osteoblasts to form new bone. The prior art may teach that 2-methylene vitamin D compounds can be used to increase bone calcium mobilization (*i.e.*, resorption), but the prior art does not teach that 2MD can be used to stimulate osteoblasts to form new bone. Thus, "improvement of bone grafts" as stated in the cited references clearly refers to improving the remodeling phase of bone healing and the ***quality*** of new bone, not the reparative phase of bone healing to increase rate of skeletal repair.

The Office Action does not appreciate fully the distinction between therapeutic agents that "grow ***new*** bone" versus agents that "increase bone mineral content." Repairing a fracture requires growing new bone structure that fills the void created at the fracture (*i.e.*, new bone growth on the surface of quiescent bone). These steps occur early in the bone healing process. In contrast, a disease such as osteoporosis (from the Greek for "holes in the bone") may be treated by increasing the mass and density of existing bone (*e.g.*, by increasing bone mineralization content of existing bone as occurs in remodeling). Therapeutic agents for treating osteoporosis include remodeling agents that improve existing bone mineralization or cause inner spaces of existing bone to become filled with bone structure (*e.g.*, resorption-blocking agents such as estrogen and bisphophonates). Such therapeutic agents would not necessarily be expected to increase rate of skeletal repair by stimulating osteoblast cells to form new bone. Although 2MD was observed previously to increase bone mineralization content, this is not the same as having observed stimulation of ***new*** bone growth.

For all these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are requested.

VI. Claim Rejections – 35 U.S.C. § 103 – DeLuca WO '98 in view of Chin

Claims 1 and 26-28 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over DeLuca WO '98 as applied to claims 1-5 and 8-11 further in view of Chin (U.S. Patent No. 5,976,142). The Applicants respectfully traverse the rejection in view of the foregoing claim amendments and for the following reasons.

Claims 26-28 have been cancelled. The pending claims have been amended effectively to incorporate the limitations of claims 6, 7, 24, and 25.

For these reasons, reconsideration and withdrawal of the rejection are requested.

VII. Conclusion

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,
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